REMARKS

Introductory Comments:

Claims 1-35 were pending in the application. Applicants note with appreciation that the Office has acknowledged applicants' election of Group II, claims 24-29, as provided for in the Response filed 20 December 2001. As a result, claims 1-23 and 30-35 have been withdrawn from further consideration pursuant to 37 C.F.R. § 1.142(b) as drawn to a non-elected invention.

Accordingly, claims 24-29 are currently under consideration and were examined in the Office Action dated 21 March 2002. In the Action, the Office has asserted an objection to the drawings as detailed in the Form PTO 948; and has asserted the following claim rejections: (1) claims 24-29 stand rejected under 35 U.S.C. §103(a) as unpatentable over International Publication No. WO 99/27961 to Sarphie et al ("Sarphie") in view of McCluskie et al. (1998) *J. Immunol.* 161:4463-4466 ("McCluskie"); and (2) claims 24-29 stand rejected under 35 U.S.C. §103(a) as unpatentable over International Publication No. WO 98/20734 to Glenn et al. ("Glenn") in view of McCluskie. The objections to the drawings are believed to have been overcome by the present submissions, and the rejections to the claims are traversed for the following reasons.

Overview of the Amendment:

Applicants, by way of this response, have entered minor amendments to Figures 8A-8D and 10A-10C. More particularly, applicants have re-labeled the figures so that each view is labeled separately in accordance with the Draftperson's request. Applicants have provided herewith new drawing sheets 8/13 and 10/13

including the properly labeled figures in "clean" copy, and have further provided drawing sheets 8/13 and 10/13 with the changes highlighted in "marked-up" copy. No new matter has been added by way of these minor drawing amendments, and the entry thereof is respectfully requested.

The Objection to the Drawings:

The Draftperson has objected to applicants' Figures 8A-8D and 10A-10C under 37 C.F.R. §1.84(h) on the basis that views are not labeled separately (see Form PTO 948 attached to the current Official Action). Applicants were required to submit drawing corrections within the time period set by the current Official Action (37 C.F.R. §1.85(a)). In response, applicants have amended the drawings to provide separate labeling for the various views. Reconsideration and withdrawal of the objection to the drawings is thus respectfully requested.

The Rejections under 35 U.S.C. §103:

Claims 24-29 stand rejected under 35 U.S.C. §103(a) as unpatentable over Sarphie in view of McCluskie. In particular, the Office asserts that "Sarphie disclose particulate vaccine compositions for transdermal delivery. The vaccine composition comprises antigens ... and a CpG oligonucleotide, see claims 25-41. Sarphie differs from the claimed invention because the reference does not teach the use of cholera toxin (CT) in their particulate vaccine composition." The Office then asserts "the McCluskie reference discloses subunit vaccine administered intranasally in mice to induce an immune response against Hepatitis B surface antigen. It is taught that CpG motifs and CT act synergistically, resulting in stronger immune response than either adjuvant administered alone." The Office then concludes, "it would have been *prima*

facie obvious to one of ordinary skill in the art to include administration of CT along with CpG in Sarphie's particulate vaccine because McCluskie teaches that CT and CpG motifs act synergisistically to achieve a potent mucosal response." Office Action at pages 2-3. Applicants respectfully disagree.

Section 2143 of the M.P.E.P. sets forth the following three basic requirements for *prima facie* obviousness: (1) there must be some suggestion or motivation to modify or combine the references; (2) there must be a reasonable expectation of success for the modification and/or combination; and (3) the prior art reference must teach or suggest all the claim limitations. When assessing these issues, (1) the claimed invention must be considered as a whole; (2) the references must be considered as a whole and must suggest the desirability of making the combination; (3) the references must be viewed without the benefit of impermissible hindsight; and (4) a reasonable expectation of success is the standard with which obviousness is determined. *Hodosh v. Block Drug Co., Inc.*, 229 USPQ 182, 187, n.5 (Fed. Cir. 1986). Applicants submit that the Office has failed to satisfy these criteria, and has thus failed to establish *prima facie* obviousness over the combination of Sarphie with McCluskie.

Claims 24-29 recite specific compositions having the following expressly recited characteristics: (a) the compositions are particulate; (b) the compositions are suitable for delivery into or across skin; (c) the composition contains an antigen; (d) the composition contains an ADP-ribosylating toxin as an adjuvant; and (e) the composition contains a CpG oligonucleotide. It is this expressly recited combination of elements that constitutes the claimed invention as a whole, not the constituent parts of the combination. In other words, the vaccine composition has three important constituents (the antigen of interest, CT used as an adjuvant and

CpG oligonucleotides) and further displays important physical properties (it is particulate and can be delivered across skin tissue). Thus, a proper assessment of obviousness under Section 103 entails a careful consideration of the recited combination as a whole and not in discrete parts, and asks whether the cited art, considered as a whole, suggested the specific combination, and whether there was a reasonable expectation of success for the suggested combination. Applicants submit that the Office has failed in each of these essential steps.

The Primary reference to Sarphie teaches particulate vaccine compositions where a single adjuvant has been "coadministered" with the vaccine of interest. In the examples where antigen and adjuvant were delivered (Examples 4 and 5, pages 69-70), discrete antigen and adjuvant compositions were produced, and then a single adjuvant composition was administered in combination with a single antigen composition. As the Office has correctly noted, there is nothing in Sarphie to teach or suggest the use of a composition containing three essential components, that is, an antigen of interest, CT as an adjuvant and CpG oligonucleotides.

The secondary reference to McCluskie teaches direct administration of a liquid vaccine composition to a nasal mucosal surface. Thus, McCluskie's compositions are not dry particulate compositions, and certainly are not intended for delivery to skin. In addition, the skilled artisan reading the McCluskie reference would know and understand that the cholera toxin (CT) is a well-characterized mucosal delivery system. The CT molecule is made up of two parts, the A subunit and the B subunit. The B subunit is present in the toxin as a pentamer and binds to certain cell surface molecules that are commonly expressed on mucosal lining, the target tissue of the *V. cholera* infectious agent. The binding of the B subunit pentamer to the target cell facilitates insertion of the active toxin, the A subunit, into

the cell. In 1999, numerous groups were using CT molecules as a mucosal delivery system (e.g., oral delivery systems) in order to deliver antigens that would not otherwise cross mucosal membranes, or would only cross the mucosal membranes in an inefficient manner.

Applicants' recited particulate compositions are administered using a proprietary particle acceleration technique, where small particles are accelerated to very high velocity in order to obtain sufficient force to penetrate a target skin tissue. Accordingly, a ballistic delivery system is used as the delivery system, not a CT mucosal tissue binding delivery system. Applicants also deliver exclusively to the skin. Accordingly, contrary to the Office's assertions, the skilled artisan would not have been motivated to combine the Sarphie single adjuvant co-administration technique with McCluskie's liquid compositions (that were expressly designed for mucosal delivery) and then somehow magically arrive at applicants' recited compositions. The compositions are totally different from a physical perspective (particulate versus liquid) and targeted to different tissue (skin versus mucosal). Thus, when Sarphie and McCluskie are considered as a whole for what they would fairly suggest to the skilled artisan, it is clear that no skilled artisan would have been motivated to make the combination as suggested by the Office.

Since there was no sensible combination of the Sarphie and McCluskie compositions (a particulate composition and a liquid composition) in such a way as to arrive at applicants' specific particulate combination, the recited compositions were not taught or suggested by the art and applicants' claims cannot have been obvious over this combination of documents. In addition, since the combination was neither taught nor suggested by the prior art, there cannot have been a reasonable expectation of success for the combination. For all of these reasons,

then, the rejection of claims 24-29 under 35 U.S.C. §103(a) over Sarphie and McCluskie is improper. Reconsideration and withdrawal of the rejection is thus earnestly solicited.

Claims 24-29 stand rejected under 35 U.S.C. §103(a) as unpatentable over the combination of Glenn in view of McCluskie. In particular, the Office asserts "Glenn discloses particulate vaccine compositions for transcutaneous immunization that does not perforate the skin. The vaccine composition comprises antigens and nucleic acids encoding antigens, and an ADP-ribosylating exotoxin, CT. Glenn differs from the claimed invention because the reference does not teach the use of CpG motif adjuvant in their particulate vaccine composition." The Office goes on to argue the teachings of McCluskie (synergistic CT and CpG responses), and then concludes "it would have been *prima facie* obvious to one of ordinary skill in the art to include administration of CpG along with CT in Glenn's particulate vaccine." Office Action at page 4. Applicants respectfully disagree.

Contrary to the Office's assertions, Glenn does not disclose a particulate composition. In this regard, the topical compositions described by Glenn include: creams; emulsions; gels; lotions; ointments; pastes; solutions; or suspensions (see Glenn at page 10, lines 1-11). The compositions actually taught and used by Glenn are almost exclusively an "immunizing solution," that is, a liquid formulation (see Examples 1-11, 13-17, 19-26, and 28-30). Alternatively, a liposomal formulation (Example 12) or a cream (Example 27) seem to have been used.

In addition, Glenn clearly identifies the cell surface binding activity of the CT molecule, where full CT or B subunit were found to work in the topical studies due to some binding mechanism (see Glenn at page 15, lines 4-15). Accordingly, Glenn is clearly using the CT molecule as a delivery mechanism.

As discussed herein above, McCluskie is directly exclusively to liquid compositions applied to mucosal surfaces. Accordingly, the combination of Glenn in view of McCluskie clearly fails to teach or suggest applicants particulate vaccine compositions. For these reasons, then, the rejection of claims 24-29 under 35 U.S.C. §103(a) over the combination of Glenn and McCluskie is improper. Reconsideration and withdrawal of the rejection is earnestly solicited.

CONCLUSION

Applicants submit that the claims define an invention which is both novel and nonobvious over the prior art. Accordingly, a Notice of Allowance is believed in order and the issuance of such a notice is respectfully requested. Applicants further ask that, should the Examiner note any minor remaining issues that may be resolved with a telephone call, that he contact the undersigned in the UK at +44 1865 332 600.

Respectfully submitted,

Date: 23 September 2002

By: _____
Thomas P. McCracken
Registration No 38,548

POWDERJECT PHARMACEUTICALS PLC
Florey House
The Oxford Science Park
Oxford OX4 4GA
United Kingdom
Telephone: +44 1865 332 600
Fax: +44 1865 332 601